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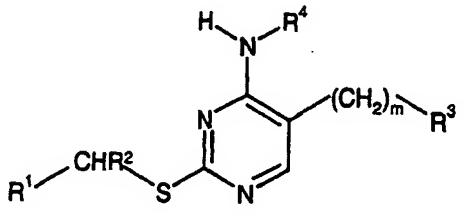
(54) Title: 4-AMINOPYRIMIDINE DERIVATIVES



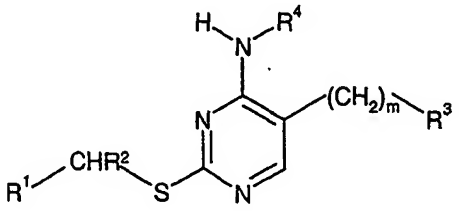
(I)

(57) Abstract: This invention relates to 4-aminopyrimidine derivatives of the general formula (I) wherein R^1, R^2, R^3 and R^4 have the signifiances defined in the specification and their pharmaceutically acceptable salts. The invention further relates to the preparation of such compounds, to medicaments containing such compounds and to their use for the prevention or treatment of mGluR5 receptor mediated disorders.

Case 20881

4-Aminopyrimidine Derivatives

The present invention relates to 4-aminopyrimidine derivatives of the general formula



I

wherein

R^1 signifies C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, -C(O)O-CH_2-heteroaryl, wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl, or unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen;

R^2 signifies hydrogen or C_1-C_6-alkyl;

R^3 signifies unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, or unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, or -C(O)O-(C_1-C_6)-alkyl;

R^4 signifies hydrogen or C_1-C_6-alkyl; and

m is 0, 1 or 2;

as well as pharmaceutically acceptable salts thereof.

It has now surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment or prevention of mGluR5 receptor mediated disorders.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

Glutamate is the major excitatory neurotransmitter in the brain and plays a unique role in a variety of central nervous system (CNS) functions. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group, namely the ionotropic receptors, forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein coupled receptors.

At present, eight different members of these mGluR are known and of these some even have sub-types. According to their sequence homology, signal transduction mechanisms and agonist selectivity, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are ischemia, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions.

Disorders mediated full or in part by mGluR5 are for example acute, traumatic and chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression and pain.

Selective mGluR5 antagonists are especially useful for the treatment of anxiety and pain.

Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts, the above-mentioned compounds as pharmaceutically active substances and their production. Further objects of the invention are medicaments based on a compound in accordance with the invention and their manufacture as well as the use of the compounds in the control or prevention of mGluR5 receptor mediated disorders, and, respectively, for the production of corresponding medicaments.

The following definitions of general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. The term "(C_{1-6})-alkyl" ("lower alkyl") used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and the like.

The terms "C_2-C_6-alkenyl" or "C_2-C_6-alkinyl" denote straight-chain or branched unsaturated hydrocarbon residues with 2 to 6 carbon atoms, preferably with 2 to 4 carbon atoms, such as ethenyl, ethinyl, 1-propenyl, 2-propenyl, propargyl, 1-butenyl and the like.

The term "C_3-C_6-cycloalkyl" means a cycloalkyl group containing 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "halogen" denotes fluorine, chlorine, bromine and iodine.

"Aryl" represents an aromatic carbocyclic group consisting of one individual ring, or one or more fused rings in which at least one ring is aromatic in nature. Preferred aryl groups are phenyl or naphthyl.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring containing one or more heteroatoms selected from nitrogen, oxygen or sulphur, or to a bicyclic aromatic group comprising two 5- or 6-membered rings, in which one or both rings can contain one or more heteroatoms selected from nitrogen, oxygen or sulphur. Examples of such heteroaryl goups are furyl, pyrrolyl, thienyl (thiophenyl), 1H-imidazolyl, 2H-imidazolyl,

4H-imidazolyl, 1H-pyrazolyl, 3H-pyrazolyl, 4H-pyrazolyl, 1,2-oxazolyl, 1,3-oxazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, [1,2,4]oxadiazolyl, [1,3,4]oxadiazolyl, [1,2,3]oxadiazolyl, tetrazolyl, [1,2,3,4]oxatriazolyl, [1,2,3,5]oxatriazolyl, 1,3-thiazolyl, 1,2-thiazolyl, pentazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzofuryl (benzofuranyl), benzothienyl (benzothiophenyl), benzimidazolyl, benzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, quinolyl, isoquinolyl and their dihydro derivatives.

Preferred heteroaryl groups are furyl, pyrrolyl and thienyl as well as [1,2,4]oxadiazolyl or isoxazolyl.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base.

Preferred compounds of formula I are those, in which m is 0 or 1. Especially preferred are those compounds, in which m is 1.

More preferred are compounds of formula I, in which m is 1 and R^3 signifies unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano.

Even more preferred are compounds of formula I, in which m is 1, R^3 signifies unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, and R^1 is -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, or -C(O)O-CH_2-heteroaryl wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl.

The following are examples of such compounds:
(4-amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid methyl ester,
(4-amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
[4-amino-5-(1-methyl-1H-pyrrol-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
2-(4-amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-propionic acid methyl ester,
(4-amino-5-thiophen-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
(4-amino-5-furan-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
[4-amino-5-(3-methyl-thiophen-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
[4-amino-5-(5-chloro-thiophen-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
[4-amino-5-(5-ethyl-furan-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,

[4-amino-5-(5-methyl-furan-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester, (4-ethylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester, and (4-isobutylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester.

Further preferred are those compounds of formula I, in which m is 1, R^3 signifies unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, and R^1 signifies unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen.

2-([1,2,4]Oxadiazol-3-ylmethylsulfanyl)-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine is an example of such a compound.

Especially preferred are also compounds of formula 1, in which m is 1, R^3 signifies unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, and R^1 signifies C_2-C_6-alkenyl, C_2-C_6-alkinyl or C_3-C_6-cycloalkyl.

Examples for such compounds are
2-prop-2-ynylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine,
2-allylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine, and
2-cyclopropylmethylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine.

Also preferred are compounds of formula I, in which m is 1 and R^3 is unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano.

Especially preferred are compounds of formula I, in which m is 1, R^3 is unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, and R^1 is -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, or -C(O)O-CH_2-heteroaryl wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl.

The following are examples of such compounds:
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
[4-amino-5-(4-bromo-benzyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid allyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid prop-2-ynyl ester,

(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 2-methyl-cyclopropylmethyl ester,

(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutylmethyl ester,

(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutyl ester,

(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopentyl ester,

(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 5-methyl-isoxazol-3-ylmethyl ester,

(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopropylmethyl ester, and

(4-amino-5-benzyl-pyrimidin-2-yloxy)-acetic acid methyl ester.

Preferred compounds of formula I are also those, in which m is 1, R^3 is unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, and R^1 is unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen.

5-Benzyl-2-(3-cyclopropyl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)-pyrimidin-4-ylamine is an example of such a compound.

Further preferred compounds of formula I are those, in which m is 1, R^3 is unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, and R^1 is C_2-C_6-alkenyl, C_2-C_6-alkinyl or C_3-C_6-cycloalkyl.

4-(2-Allylsulfanyl-4-amino-pyrimidin-5-ylmethyl)-benzonitrile is an example of such a compound.

Also preferred are compounds of formula I, in which m is 1 and R^3 signifies C_3-C_6-cycloalkyl.

An example of such a compound is (4-amino-5-cyclopropylmethyl-pyrimidin-2-yl-sulfanyl)-acetic acid ethyl ester.

Further preferred compounds of formula I are those, in which m is 0. Especially preferred are those, in which m is 0 and R^1 is -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, or -C(O)O-CH_2-heteroaryl wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl.

The following are examples of such compounds:

[4-amino-5-(2,4-dichloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,

4-amino-2-ethoxycarbonylmethylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester, and [4-amino-5-(2-chloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester.

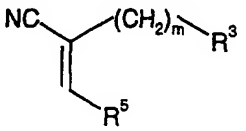
Preferred compounds of formula I are those, in which R^2 signifies hydrogen.

Also preferred are compounds of formula I, wherein R^4 signifies hydrogen.

Preferred compounds of formula I are also those, wherein R^3 signifies a heteroaryl group selected from furyl, pyrrolyl and thienyl which is optionally substituted by substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano.

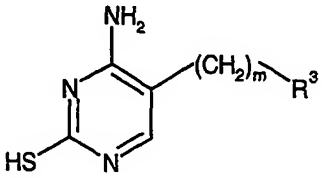
Also preferred are compounds of formula I, wherein R^1 signifies [1,2,4]oxadiazolyl optionally substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen.

The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by
reacting a compound of formula



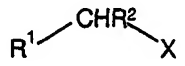
II

wherein R^5 signifies phenylamino, 3-thienylamino or morpholino, and R^3 and m have the significances as defined before,
with thiourea to obtain a compound of formula



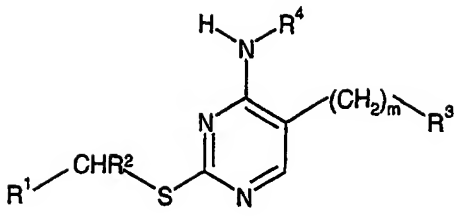
III

and reacting this compound with a compound of formula



IV

wherein R^1 and R^2 have the significances as defined before and X is halogen,
and, if desired, converting the amino group into an aminoalkyl group, to obtain a compound of formula

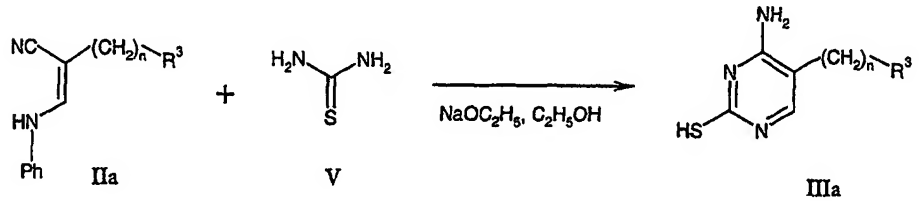


I

wherein R^4 is hydrogen or C_1-C_6-alkyl,
and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

In accordance with the invention, a 4-aminopyrimidine derivative of formula III is formed by condensation of thiourea (1.1 eq.) with an appropriately substituted compound of formula II. Compounds of formula III, wherein m signifies 1 or 2, are prepared from thiourea and a 2-substituted 3-phenylamino-acrylonitrile. The condensation reaction is carried out in ethanol under reflux using a catalytic amount of a strong base like sodium ethoxide (e.g. 0.1 eq). The product can be obtained as precipitate after reducing the solvent and cooling (Scheme 1).

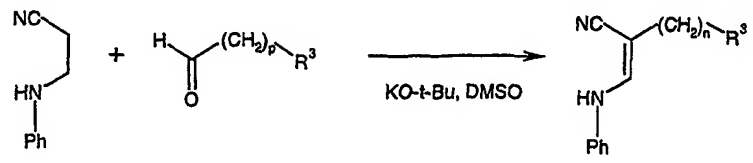
Scheme 1



IIa V IIIa

The 2-substituted 3-phenylamino-acrylonitrile of formula IIa, wherein n is 1 or 2, is prepared by condensation of an aldehyde of formula VII, wherein p is 0 or 1, with β-anilinopropionitrile (VI) (scheme 2). Treatment of a solution of VII and VI in dimethylsulfoxide with strong base like potassium-tert-butylate (1 eq.) gives the condensation product IIa.

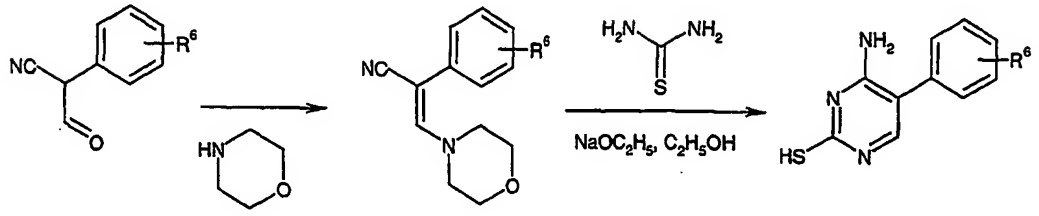
Scheme 2



VI VII IIa

4-Aminopyrimidines of formula III, wherein m signifies 0, are obtained by the procedures described in schemes 3 and 4.

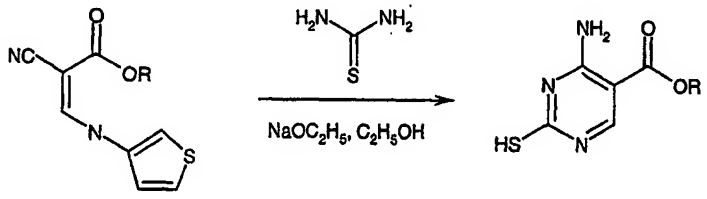
Scheme 3



VIII IIb IIIb

For example, compounds of formula IIIb are prepared by reacting a 2-formyl-2-phenylacetonitrile of formula VIII with morpholine followed by condensation of the obtained 3-morpholino-2-phenylacrylonitrile of formula IIb with thiourea (scheme 3).

Scheme 4

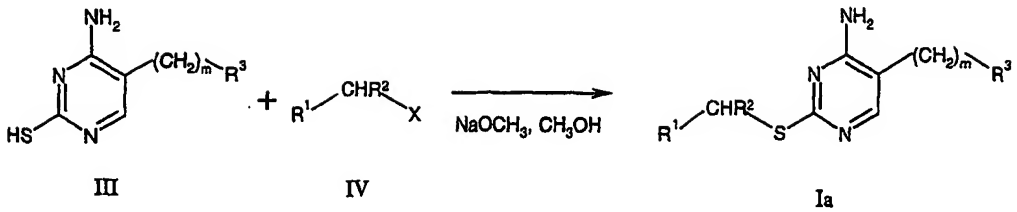


IIc IIIc

A 4-amino-2-sulfanyl-pyrimidine-5-carboxylic acid ester of formula IIIc is obtained by condensation of a 2-cyano-3-(3-thienylamino)-2-propenoic acid ester of formula IIc with thiourea (scheme 4).

The reaction of the 5-substituted 4-amino-pyrimidine-2-thiols of formula III with appropiate alkyl halides of formula IV leads to the corresponding 5-substituted 2-alkylsulfanyl-pyrimidin-4-ylamines of formula Ia. The reaction is carried out at room temperature in a 1M solution of sodium methoxide in methanol or of sodium ethoxide in ethanol (scheme 5).

Scheme 5

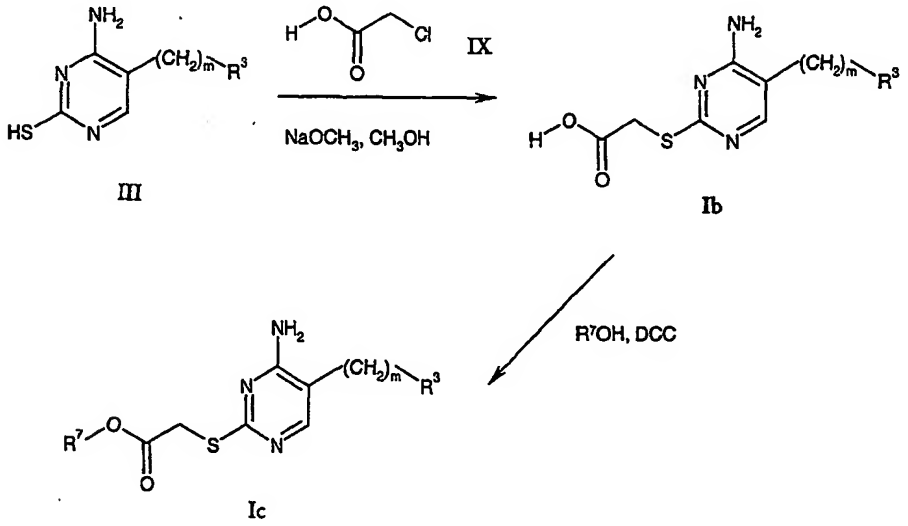


III IV Ia

Compounds of formula I, wherein R^1 is alkoxycarbonyl and R^2 is hydrogen, are prepared by either directly reacting a compound of formula III with an alkyl bromoacetate or by the procedure as described in scheme 6.

A 5-substituted (4-amino-pyrimidin-2-ylsulfanyl)-acetic acid of formula Ib is obtained by reacting a compound of formula III with 2-chloro-acetic acid IX. Esterification of Ib with dicyclohexylcarbodiimide (DCC) and the appropiate alcohol R^7OH, in which R^7 is (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkinyl, (C_3-C_6)-cycloalkyl, -CH_2-(C_3-C_6)-cycloalkyl or -CH_2-heteroaryl wherein the heteroaryl ring may be substituted by one or more (C_1-C_6)-alkyl, leads to the ester of formula Ic.

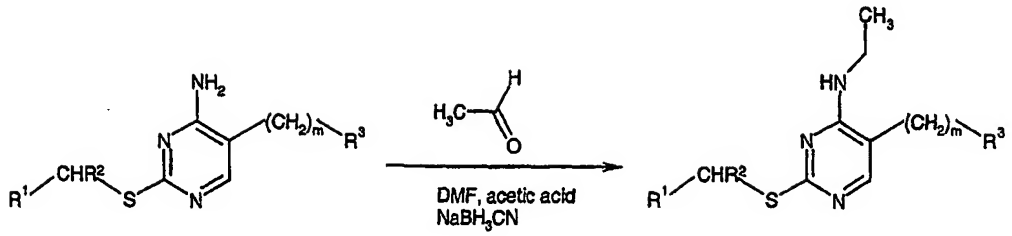
Scheme 6



III Ib Ic

Compounds of formula I, wherein R^4 signifies C_1-C_6-alkyl are prepared by reacting the amine of formula Ia with an appropriate aldehyde. For example, a compound of formula Id, wherein R^4 is ethyl, is obtained by the reaction of a compound of formula Ia with acetaldehyde and reduction with sodium cyanoborohydride (scheme 7).

Scheme 7



Ia Id

Pharmaceutically acceptable salts of coumpounds of formula I can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, cognitive disorders and memory deficits, as well as acute and chronic pain. Treatable neurological disorders are for instance epilepsy, schizophrenia, anxiety, acute, traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Huntington's chorea, ALS, multiple sclerosis, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia.

The compounds of formula I and their pharmaceutically acceptable salts are especially useful as analgesics. Treatable kinds of pain include inflammatory pain auch as arthritis and rheumatoid disease, vasculitis, neuropathic pain such as trigeminal or herpetic neuralgia, diabetic neuropathy pain, causalgia, hyperalgesia, severe chronic pain,

post-operative pain and pain associated with various conditions like cancer, angina, renal or billiay colic, menstruation, migraine and gout.

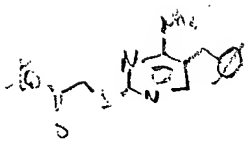
The pharmacological activity of the compounds was tested using the following method:

cDNA encoding rat mGlu 5a receptor was transiently transfected into EBNA cells using a procedure described by E.-J. Schlaeger and K. Christensen (*Cytotechnology* 1998, 15, 1-13). $[Ca^{2+}]i$ measurements were performed on mGlu 5a transfected EBNA cells after incubation of the cells with Fluo 3-AM (obtainable by FLUKA, 0.5 µM final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. $[Ca^{2+}]i$ measurements were done using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation, La Jolla, CA, USA). When compounds were evaluated as antagonists they were tested against 10 µM glutamate as agonist.

The inhibition (antagonists) curves were fitted with a four parameter logistic equation giving IC_{50}, and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

The compounds of the present invention are mGluR 5a receptor antagonists. The activities of compounds of formula I as measured in the assay described above are in the range of 10 µM or less, typically of 1 µM or less, and ideally of 0.2 µM or less.

In the table below are shown specific activity data of preferred compounds of formula I as measured in the assay described above:



Example No.	Compound name	IC_{50} (µM)
3	(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester	0.14
4	[4-amino-5-(1-methyl-1H-pyrrol-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester	0.38
5	[4-amino-5-(2,4-dichloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester	3.85
6	[4-amino-5-(4-bromo-benzyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester	0.18
8	2-prop-2-ynylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine	1.39
9	2-allylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine	2.79
11	2-([1,2,4]oxadiazol-3-ylmethylsulfanyl)-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine	0.4
12	(4-amino-5-thiophen-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester	0.18

13	(4-amino-5-furan-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester	0.16
19	4-amino-2-ethoxycarbonylmethylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester	0.27
21	(4-ethylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester	0.6
22	(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid allyl ester	0.12
24	(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 2-methyl-cyclopropylmethyl ester	0.63
Example No.	Compound name	IC_{50} (μM)
25	(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutylmethyl ester	1.46
29	(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopropylmethyl ester	0.2
31	4-isobutylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester	0.16
32	5-benzyl-2-(3-cyclopropyl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)-pyrimidin-4-ylamine	0.45

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula IA or IB or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula IA or IB or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Examples

General Procedure A

Synthesis of 2-substituted 3-phenylamino-acrylonitriles

Potassium-tert-butylate (1 eq.) is added to a cooled (10 °C) solution of 3-phenylamino-propionitrile (1 eq.) and an aldehyde (1 eq.) in DMSO (approx. 0.3M). After stirring for 3 hours at r.t., the mixture is cooled in an ice bath and water is added. The mixture is extracted several times with diethylether, the combined organic phases are dried over $MgSO_4$, and most of the solvent is evaporated under reduced pressure. The 2-substituted 3-phenylamino-acrylonitrile crystallizes from the remaining solvent and is sufficiently pure for further conversion according to general procedure B.

General Procedure B

Synthesis of 5-substituted 4-amino-pyrimidine-2-thiols

A catalytic amount (e.g. 0.1 eq.) of sodium ethoxide is added to a solution of 2-substituted 3-phenylamino-acrylonitrile (1 eq.) as prepared according to general

procedure A and thiourea (1.1 eq.) in ethanol which is then heated to reflux. After 6h, a drop of formic acid is added and approximately half of the solvent is evaporated under reduced pressure. The mixture is then placed in a refrigerator (4 °C) overnight. The precipitated 5-substituted 4-amino-pyrimidine-2-thiol is collected and purified, e.g. by crystallisation from EtOH or by column chromatography.

General Procedure C

Synthesis of 5-substituted 2-Alkylsulfanyl-pyrimidin-4-ylamines

5-substituted 4-amino-pyrimidine-2-thiol is dissolved in 1M sodium methoxide solution in methanol or 1M sodium ethoxide solution in ethanol (1 eq.). After addition of an alkyl halide (2 eq.), the mixture is stirred for 90 min at r.t.. Formic acid (1 eq.) is added and the 5-substituted 2-alkylsulfanyl-pyrimidin-4-ylamine is isolated from the mixture, e.g. by HPLC chromatography (YMC CombiPrep C18 column 50x20 mm, solvent gradient 10-95% CH_3CN in 0.1% TFA(aq) over 6.0 min, λ = 230 nm, flow rate 40 ml/min).

Example 1

(4-Amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid methyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 295.7 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and methyl bromoacetate.

Example 2

(4-Amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 309.7 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and ethyl bromoacetate.

Example 3

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 303.8 ($M+H^+$), was prepared using benzaldehyde and ethyl bromoacetate.

Example 4

[4-Amino-5-(1-methyl-1H-pyrrol-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 306.8 ($M+H^+$), was prepared using 1-methylpyrrole-2-carboxaldehyde and ethyl bromoacetate.

Example 5

[4-Amino-5-(2,4-dichloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

a) 2-(2,4-Dichloro-phenyl)-3-piperidin-1-yl-acrylonitrile

2-(2,4-Dichloro-phenyl)-3-piperidin-1-yl-acrylonitrile was prepared according to the method as described in *Tetrahedron* 1972, *28*, 1343.

b) 4-Amino-5-(2,4-dichloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures B and C, the title compound, MS: m/e = 358.0 ($M+H^+$), was prepared using 2-(2,4-dichloro-phenyl)-3-piperidin-1-yl-acrylonitrile and ethyl bromoacetate.

Example 6

[4-Amino-5-(4-bromo-benzyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 382.0 ($M+H^+$), was prepared using 4-bromobenzaldehyde and ethyl bromoacetate.

Example 7

2-(4-Amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-propionic acid methyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 310.2 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and 2-bromo-propionic acid methyl ester.

Example 8

2-Prop-2-ynylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine

Following general procedures A, B, and C, the title compound, MS: m/e = 262.0 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and propargyl bromide.

Example 9

2-Allylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine

Following general procedures A, B, and C, the title compound, MS: m/e = 264.0 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and allyl bromide.

Example 10

2-Cyclopropylmethylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine

Following general procedures A, B, and C, the title compound, MS: m/e = 278.0 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and bromomethyl-cyclopropane.

Example 11

2-([1,2,4]Oxadiazol-3-ylmethylsulfanyl)-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine

Following general procedures A, B, and C, the title compound, MS: m/e = 306.0 ($M+H^+$), was prepared using 2-thiophenecarbaldehyde and 3-chloromethyl-[1,2,4]oxadiazole.

Example 12

(4-Amino-5-thiophen-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 310.0 ($M+H^+$), was prepared using 3-thiophenecarbaldehyde and ethyl bromoacetate.

Example 13

(4-Amino-5-furan-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 294.0 ($M+H^+$), was prepared using 3-furancarbaldehyde and ethyl bromoacetate.

Example 14

[4-Amino-5-(3-methyl-thiophen-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 324.0 ($M+H^+$), was prepared using 3-methyl-thiophene-2-carbaldehyde and ethyl bromoacetate.

Example 15

[4-Amino-5-(5-chloro-thiophen-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 344.0 ($M+H^+$), was prepared using 5-chloro-thiophene-2-carbaldehyde and ethyl bromoacetate.

Example 16

[4-Amino-5-(5-ethyl-furan-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 322.0 ($M+H^+$), was prepared using 5-ethyl-furan-2-carbaldehyde and ethyl bromoacetate.

Example 17

[4-Amino-5-(5-methyl-furan-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 308.0 ($M+H^+$), was prepared using 5-methyl-furan-2-carbaldehyde and ethyl bromoacetate.

Example 18

4-(2-Allylsulfanyl-4-amino-pyrimidin-5-ylmethyl)-benzonitrile

Following general procedures A, B, and C, the title compound, MS: m/e = 283.0 ($M+H^+$), was prepared using 4-formyl-benzonitrile and allyl bromide.

Example 19

4-Amino-2-ethoxycarbonylmethylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester

Following general procedures B and C, the title compound, MS: m/e = 286.0 ($M+H^+$), was prepared using ethyl 2-cyano-3-(3-thienylamino)-acrylate and ethyl bromoacetate.

Example 20

[4-Amino-5-(2-chloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

a) 2-(2-Chloro-phenyl)-3-piperidin-1-yl-acrylonitrile

2-(2-Chloro-phenyl)-3-piperidin-1-yl-acrylonitrile was prepared in analogy to the method as described in *Tetrahedron* 1972, *28*, 1343.

b) [4-Amino-5-(2-chloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester

Following general procedures B and C, the title compound, MS: m/e = 324.0 ($M+H^+$), was prepared using 2-(2-chloro-phenyl)-3-piperidin-1-yl-acrylonitrile and ethyl bromoacetate.

Example 21

(4-Ethylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

To a solution of (4-Amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester (0.5mmol, 155mg) as prepared in example 12 and acetaldehyde (0.6mmol, 27mg) in 1.25ml of DMF was added acetic acid (0.25ml) and sodium cyanoborohydride (0.6mmol, 38mg) and the mixture was shaken for two days at r.t.. The title compound, MS: m/e = 338.2 ($M+H^+$), was obtained from the mixture by HPLC chromatography (YMC CombiPrep C18 column 50x20 mm, solvent gradient 10-95% CH_3CN in 0.1% TFA(aq) over 6.0 min, λ = 230 nm, flow rate 40 ml/min).

Example 22

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid allyl ester

a) (4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid was obtained from 4-amino-5-benzyl-pyrimidine-2-thiol in analogy to the method in *J. Org. Chem.* 1956, *21*, 567. 4-Amino-5-benzyl-pyrimidine-2-thiol was prepared according to general procedures A and B using benzaldehyde.

b) (4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid allyl ester

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid (0.25 mmol, 69 mg), dicyclohexylcarbodiimide (0.3 mmol, 62 mg) and allyl alcohol (0.3 mmol, 18 mg) were dissolved in 1 ml of DMF, and a catalytic amount of 4-dimethylaminopyridine (approx. 1 – 3 mg) was added. After shaking the mixture for 24h at r.t., the title compound, MS: m/e = 316.2 ($M+H^+$), was obtained from the reaction mixture by HPLC chromatography (YMC CombiPrep C18 column 50x20mm, solvent gradient 10-95% CH_3CN in 0.1% TFA(aq) over 6.0min, λ = 230 nm, flow rate 40 ml/min).

Example 23

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid prop-2-ynyl ester

The title compound, MS: m/e = 314.0 ($M+H^+$), was prepared from propargyl alcohol in analogy to the method described in example 22.

Example 24

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 2-methyl-cyclopropylmethyl ester

The title compound, MS: m/e = 343.9 ($M+H^+$), was prepared from (2-methyl-cyclopropyl)-methanol in analogy to the method described in example 22.

Example 25

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutylmethyl ester

a) Cyclobutylmethanol

Cyclobutylmethanol was prepared according to the method as described in *J. Chem. Soc. Perkin Trans. 1*; 1993; *7*, 801-804.

b) 4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutylmethyl ester

The title compound, MS: m/e = 343.9 ($M+H^+$), was prepared from cyclobutylmethanol in analogy to the method described in example 22.

Example 26

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutyl ester

The title compound, MS: m/e = 330.0 ($M+H^+$), was prepared from cyclobutanol in analogy to the method described in example 22.

Example 27

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopentyl ester

The title compound, MS: m/e = 344.0 ($M+H^+$), was prepared from cyclopentanol in analogy to the method described in example 22.

Example 28

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 5-methyl-isoxazol-3-ylmethyl ester

The title compound, MS: m/e = 371.0 ($M+H^+$), was prepared from (5-Methyl-isoxazol-3-yl)-methanol in analogy to the method described in example 22.

Example 29

(4-Amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopropylmethyl ester

The title compound, MS: m/e = 330.0 ($M+H^+$), was prepared from cyclopropylmethanol in analogy to the method described in example 22.

Example 30

(4-Amino-5-benzyl-pyrimidin-2-yloxy)-acetic acid methyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 274.0 ($M+H^+$), was prepared using benzaldehyde and methyl bromoacetate.

Example 31

4-Isobutylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

The title compound, MS: m/e = 366.0 ($M+H^+$), was prepared in analogy to the method of example 21 from isobutyraldehyde.

Example 32

(4-Amino-5-cyclopropylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester

Following general procedures A, B, and C, the title compound, MS: m/e = 267.9 ($M+H^+$), was prepared using cyclopropylcarbaldehyde and ethyl bromoacetate.

Example 33

5-Benzyl-2-(3-cyclopropyl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)-pyrimidin-4-ylamine

A solution of (4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid (0.35 mg, 1.27 mmol) as prepared according to the method described in example 22, and 1,1'-carbonyl-diimidazole (0.31 g, 1.91 mmol) in DMF (8 ml) was stirred at room temperature for 3 h and subsequently N-hydroxy-cyclopropanecarboxamidine (0.19 g, 1.91 mmol) was

added. The reaction mixture was stirred at 80°C for 20 h and evaporated. Acetic acid (10 ml) was added and the stirred mixture was heated under reflux conditions for 2 h. Aqueous work-up, column chromatography on silica gel (ethyl acetate/hexane 3:2) and crystallization from ethyl acetate/hexane yielded the title compound (36 mg, 9%) as an off-white solid, m.p. 94 °C and MS: m/e = 340.3 ($M+H^+$).

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

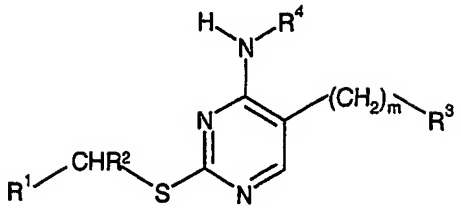
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

Claims

1. A compound of the general formula



I

wherein

R^1 signifies C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, -C(O)O-CH_2-heteroaryl, wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl, or unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen;

R^2 signifies hydrogen or C_1-C_6-alkyl;

R^3 signifies unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, or unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano, or -C(O)O-(C_1-C_6)-alkyl;

R^4 signifies hydrogen or C_1-C_6-alkyl; and

m is 0, 1 or 2;

as well as pharmaceutically acceptable salts thereof.

2. A compound of formula I in accordance with claim 1, wherein m is 0 or 1.

3. A compound of formula I in accordance with claim 1, wherein m is 1.

4. A compound of formula I in accordance with claim 3, wherein R^3 is unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano.

5. A compound of formula I in accordance with claim 4, wherein R^1 is -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, or -C(O)O-CH_2-heteroaryl wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl.

6. A compound in accordance with claim 5, which compound is selected from the group consisting of
(4-amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid methyl ester,
(4-amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
[4-amino-5-(1-methyl-1H-pyrrol-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
2-(4-amino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-propionic acid methyl ester,
(4-amino-5-thiophen-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
(4-amino-5-furan-3-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
[4-amino-5-(3-methyl-thiophen-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
[4-amino-5-(5-chloro-thiophen-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
[4-amino-5-(5-ethyl-furan-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
[4-amino-5-(5-methyl-furan-2-ylmethyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
(4-ethylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester, or
(4-isobutylamino-5-thiophen-2-ylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester.

7. A compound in accordance with claim 4, wherein R^1 is unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen.

8. A compound in accordance with claim 7, which compound is
2-([1,2,4]oxadiazol-3-ylmethylsulfanyl)-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine.

9. A compound in accordance with claim 4, wherein R^1 is C_2-C_6-alkenyl, C_2-C_6-alkinyl or C_3-C_6-cycloalkyl.

10. A compound in accordance with claim 9, which compound is selected from the group consisting of
2-prop-2-ynylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine,

2-allylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine, or
2-cyclopropylmethylsulfanyl-5-thiophen-2-ylmethyl-pyrimidin-4-ylamine.

11. A compound of formula I in accordance with claim 3, wherein R^3 is unsubstituted aryl or aryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl, halogen or cyano.

12. A compound of formula I in accordance with claim 11, wherein R^1 is -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, or -C(O)O-CH_2-heteroaryl wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl.

13. A compound in accordance with claim 12, which compound is selected from the group consisting of
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester,
[4-amino-5-(4-bromo-benzyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid allyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid prop-2-ynyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 2-methyl-cyclopropylmethyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutylmethyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclobutyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopentyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid 5-methyl-isoxazol-3-ylmethyl ester,
(4-amino-5-benzyl-pyrimidin-2-ylsulfanyl)-acetic acid cyclopropylmethyl ester, or
(4-amino-5-benzyl-pyrimidin-2-yloxy)-acetic acid methyl ester.

14. A compound in accordance with claim 11, wherein R^1 is unsubstituted heteroaryl or heteroaryl substituted by one or more C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_6-cycloalkyl or halogen.

15. A compound in accordance with claim 14, which compound is 5-benzyl-2-(3-cyclopropyl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)-pyrimidin-4-ylamine.

16. A compound in accordance with claim 11, wherein R^1 is C_2-C_6-alkenyl, C_2-C_6-alkinyl or C_3-C_6-cycloalkyl.

17. A compound in accordance with claim 16, which compound is 4-(2-allylsulfanyl-4-amino-pyrimidin-5-ylmethyl)-benzonitrile.

18. A compound in accordance with claim 3, wherein R^3 is C_3-C_6-cycloalkyl.

19. A compound in accordance with claim 18, which compound is (4-amino-5-cyclopropylmethyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester.

20. A compound in accordance with claim 1, wherein m is 0 and R^1 is -C(O)O-(C_1-C_6)-alkyl, -C(O)O-(C_2-C_6)-alkenyl, -C(O)O-(C_2-C_6)-alkinyl, -C(O)O-(C_3-C_6)-cycloalkyl or -C(O)O-CH_2-(C_3-C_6)-cycloalkyl, wherein the cycloalkyl ring may be substituted by one or more C_1-C_6-alkyl, or -C(O)O-CH_2-heteroaryl, wherein the heteroaryl ring may be substituted by one or more C_1-C_6-alkyl.

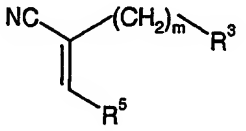
21. A compound in accordance with claim 20, which compound is selected from the group consisting of
[4-amino-5-(2,4-dichloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester,
4-amino-2-ethoxycarbonylmethylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester, or
[4-amino-5-(2-chloro-phenyl)-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester.

22. A compound in accordance with claim 1, wherein R^2 signifies hydrogen.

23. A compound in accordance with claim 1, wherein R^4 signifies hydrogen.

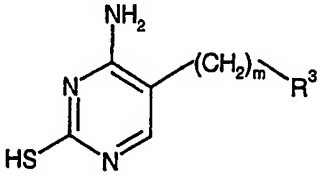
24. A process for the manufacture of a compound in accordance with claim 1 as well as its pharmaceutically acceptable salt, which process comprises

reacting a compound of formula



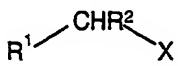
II

wherein R^5 signifies phenylamino, 3-thienylamino or morpholino, and R^3 and m have the significances as defined in claim 1,
with thiourea to obtain a compound of formula



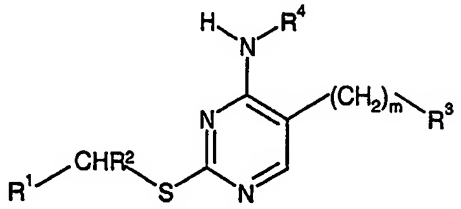
III

and reacting this compound with a compound of formula



IV

wherein R^1 and R^2 have the significances as defined in claim 1 and X is halogen, and, if desired, converting the amino group into an aminoalkyl group, to obtain a compound of formula



I

wherein R^4 is hydrogen or C_1-C_6-alkyl,
and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

25. A compound according to any one of claims 1 to 23, when manufactured by a process in accordance with claim 24.

26. A medicament containing one or more compounds as claimed in any one of claims 1 to 23 and pharmaceutically acceptable excipients for the treatment and prevention of mGluR5 receptor mediated disorders.

27. A medicament according to claim 26 for the treatment and prevention of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain.

28. A compound in accordance with any one of claims 1 to 23 as well as its pharmaceutically acceptable salt for use in the treatment or prevention of diseases.

29. The use of a compound in accordance with any one of claims 1 to 23 as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and prevention of mGluR5 receptor mediated disorders.

30. The use according to claim 29 for the manufacture of medicaments for the treatment and prevention of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain.

31. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/05379

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/46 C07D409/06 C07D403/06 C07D405/06 C07D413/06
A61K31/505 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 191 443 A (BASF) 20 August 1986 (1986-08-20) claims	1,3,22, 23
A	FR 1 013 704 A (WELLCOME) 4 August 1952 (1952-08-04) page 1, line 1-8; claims; examples	1-3,22, 23,28,31
A	EP 0 061 019 A (DYNAMIT NOBEL) 29 September 1982 (1982-09-29) claims; example 6	1,2,22, 23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 2002	05/09/2002

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/05379

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